UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,549	07/27/2001	Rainer H. Muller	662-57773	7384

20736 7590 10/20/2004

MANELLI DENISON & SELTER
2000 M STREET NW SUITE 700
WASHINGTON, DC 20036-3307

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Mail 10.19.04

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number:09/915,549
Filing Date: July 27, 2001
Appellant(s): MULLER, RAINER H.

Jeffrey S. Melcher
Reg. No. 35,950

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 08, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

The 35 U.S.C. §102(b) rejections over Davis (EPO '845) and Kaufman *et al.* (US '330) have been *withdrawn* as indicated in the Advisory Action filed 04/27/04.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 12-15, 19-63, 143, 144, 146 and 148 stand or fall together and claims 149 and 150 stand or fall together and claims 2-11 and claims 64-66 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,616,330	KAUFMAN *et al.*	04-1997
EPO 0 296 845 A1	DAVIS *et al.*	12-1988

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

- Claims 1-15, 19-66, 143, 144, 146 and 148-150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis *et al.* (EPO 0 296 845).
- Claims 1-15, 19-66, 143, 144, 146 and 148-150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaufman *et al.* (US Pat. No. 5,616,330).

Davis et al. ('845) teach a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (see reference columns 2 line 15 through col. 4, line 35). The emulsions are stable and reduce the toxicity of the drug. Davis *et al.* teach that the invention provides an oil-in-water surfactant-stabilized emulsion of a drug, wherein the drug is poorly soluble in both oil and water (col. 2, lines 15-19).

The drug used in this instance is the antibiotic, Amphotericin B. However, the drug may be any selected from a general or local anesthetic, hypnotic, sedative, antibiotic or anti-microbial, anti-neoplastics or immunosuppresants (col. 3, lines 3-19). The surfactant used is preferably lecithin or phosphatidyl choline. The amount of surfactant used may be from 0.5 to 10% (col. 4, lines 10-12). This range clearly meets the applicant's claimed amount of less than 15 wt.%. The amount of oil in the final emulsion taught is suitably 5% to 50%. Any pharmaceutically acceptable oil may be used, for example, soybean or safflower oil or medium

chain triglycerides or monoglycerides (col. 4, lines 3-9). The level of drug can be up to 1 mg/ml, in the case of Amphotericin B.

The emulsions are usually administered parentally, for example by continuous venous infusion or by injection, which may be intravenous, subcutaneous or intramuscular (col. 4, lines 19-31). The examples demonstrate the teachings of emulsions using Amphotericin B in various conditions. For instance, Example 1 demonstrates an intravenous emulsion with amphotericin B (50 mg), wherein the drug was dissolved in methanol (100 ml). The oil used in this case was soya oil (10 ml) and the emulsifier used was (1.2 g) egg phosphatidylcholine dispersed in 90 ml water. Other suitable emulsifiers can also be used, such as poloxamer, poloxamine series (col. 5, line 30 through col. 6, line 21). Example 3 shows emulsions of amphotericin B resulting in a small particle size of less than 200 nm average diameters. Similarly, Example 5 demonstrates emulsion droplet sizes, measured by a laser diffraction sizer, wherein majority of droplets were less than 1-micron diameter (col. 7, line 20 through col. 8, line 46).

The instant invention is drawn to a dispersion which comprises an oily phase; an aqueous phase, in the form of an oil-in-water emulsion and at least one active ingredient that is slightly or poorly soluble in the oily and aqueous phase, wherein the dispersion is free from toxicologically dangerous solvents.

Davis *et al.* explicitly teach a dispersion comprising an oil-in-water emulsion comprising a poorly soluble drug (Amphotericin B), which is administered parenterally, as similarly desired by the applicant. There is no significant distinction observed between the prior art and the instant invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Davis *et al.*, who teach an oil-in-water emulsion administered parenterally, comprising a poorly soluble drug (Amphotericin B) because Davis *et al.* teach that the emulsions are stable and reduce the toxicity of the drug. The expected result would be an improved stable dispersion for the beneficial treatment of infectious conditions.

Regarding the instantly claimed amounts, Davis *et al.* teach similar amounts and percentages as desired by the applicant. Furthermore, it would have been obvious to one of ordinary skill in the art that suitable amounts and percentages could be determined through the use of routine or manipulative experimentation. Additionally and in the absence of showing any criticality, the applicant has not shown any unexpected results that accrue from the use of the instantly claimed amounts. The prior art teaches suitable concentrations to arrive at stable emulsions.

***Kaufman** et al.* ('330) teach stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract); (col. 1, line 64 through col. 2, line 60). The oil-in-water emulsion system includes a taxine, oil, water and a surfactant. More particularly, a taxine, such as taxol is solubilized in the oil in an effective pharmaceutical amount for intravenous administration. The taxine and oil mixture forms a dispersed phase in the water. Other taxines include taxotere, spicatin and others (col. 2, lines 3-8). Kaufman teaches that the oil may be any of a number of oils, such as mineral, vegetable, animal, essential and synthetic oils, hydrocarbons, paraffin oils or mixtures thereof. Preferably the oil is rich in triglycerides, such as

safflower oil, soybean oil or mixtures thereof. Because taxol is more soluble in safflower oil than soybean oil, safflower oil is most preferred (col. 2, lines 10-15). The surfactant used may be a number of surfactants, and is usually a phospholipid, such as lecithin (col. 2, lines 15-17). The surfactant is needed to form stable emulsions.

Kaufman *et al.* teach that typically the taxine is present in an amount of about 0.1% to about 1% by weight of the emulsion. The oil is present in an amount of from about 1% to about 40% and the surfactant is present in an amount of about 0.5% to about 5% by weight of the emulsion. These ranges clearly read on the applicant's specified ranges.

The composition may also include further additives, such as glycerin, xylitol, mannitol, dextrose, Ringer's solution and sterols (col. 2, lines 23-36).

The examples demonstrate various preparations of emulsions comprising taxol. Example 1 shows results of a safflower oil solution containing 15 mg taxol/ml and 20 mg cholesterol/ml. This resulting composition is shown in Table 1. The particular ingredients used were lecithin, safflower oil, glycerin, cholesterol and taxol. Similarly, Example 2 shows the results for five different taxol formulations, wherein the mean particle sizes obtained were less than 1 nm, respectively (col. 4, line 47 through col. 6, line 46). In addition, the particle size was relatively constant over time, which further demonstrated the stability of the lipid emulsions of taxol.

The instant invention is drawn to dispersion which comprises an oily phase; an aqueous phase, in the form of an oil-in-water emulsion and at least one active ingredient that is slightly or poorly soluble in the oily and aqueous phase, wherein the dispersion is free from toxicologically dangerous solvents.

Kaufman *et al.* teach stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract). There is no significant distinction observed between the prior art and the instant invention since the prior art teaches the applicant's claimed desired objectives of a dispersion comprising an oil-in-water emulsion administered intravenously.

Furthermore, the applicant has not demonstrated any unexpected results that accrue from the instantly claimed percentages or ranges. The prior art teaches similar amounts using the same composition.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Kaufman *et al.*, who teach an oil-in-water emulsion administered for intravenous administration, comprising a poorly soluble drug (taxol) because, Kaufman *et al.* teach that such a composition would exhibit minimal side effects and successfully overcome the previous deficiencies of the prior art. The expected result would be a stabilized oil-in-water emulsion for administering taxol intravenously.

This rejection is maintained and applied to newly added claims 149 & 150.

Davis *et al.* teach a dispersion comprising an oil-in-water emulsion containing a poorly soluble active ingredient (antifungal - Amphotericin B), wherein the emulsions are administered parenterally (i.e., intravenously, subcutaneously, intramuscularly) (see reference columns 2 line 15 through col. 4, line 35). The emulsions are stable and reduce the toxicity of the drug. The oil-in-water surfactant-stabilized emulsion contains a surfactant in an amount of from 0.5 to 10% (instant claims require 0.1% - 20%).

Kaufmann *et al.* teach stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water (see abstract); (col. 1, line 64 through col. 2, line 60). The oil-in-water emulsion system includes a taxine, oil, water and a surfactant. The amount of surfactant contained in amounts of from about 0.5% to about 5%. Kaufmann *et al.* teach that the surfactant is needed to form stable emulsions.

The prior art teaches the generic concept of providing emulsions comprising poorly soluble active ingredients in stable form for intravenous administration.

(11) Response to Argument

Firstly, Appellant argued regarding the anticipation rejection of Claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144 146 and 148 under 35 U.S.C. §102(b) over Davis *et al.* (EPO 0 296 845).

Examiner points out that the 35 U.S.C. §102(b) rejection of claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144 146 and 148 under over Davis *et al.* has been *withdrawn* (see Advisory Action filed 04/27/04).

Secondly, Appellant argued regarding the anticipation rejection of Claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144 146 and 148 under 35 U.S.C. §102(b) over Kaufman *et al.* (US 5,616,330).

Examiner points out that the 35 U.S.C. §102(b) rejection of claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144 146 and 148 under over Kaufman *et al.* has been *withdrawn* (see Advisory Action filed 04/27/04).

The rejections currently maintained for pending claims 1-15, 19-66, 143, 144, 146 and 148-150 are 35 U.S.C. §103(a) rejections over Davis *et al.* (EP '845) and Kaufman *et al.* (US '330).

Appellant urges the claimed invention is not taught or suggested by Davis ('845). Appellant urges, "It is surprisingly possible to enter the supersaturated concentration range without precipitation of drug crystals during storage. This is achieved by novel production technology discovered and disclosed in the present application, for example, co-homogenization of drug powder and oil in water. In contrast, it is well known throughout the art, that supersaturation of drugs in a carrier provides an unstable composition in which the drug crystallizes out of solution over time. The cited references are in agreement with this by only teaching to use compositions containing drugs at their solubility limit."

The Examiner has not been persuaded by this argument. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). See also *In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983). In the instant case, the prior art teaches similar dispersion compositions comprising similar components as that desired by the instant invention.

Appellant urges, "At supersaturation levels, the claimed invention is able to provide a dose containing far less carrier than the prior art compositions. Thus, any undesirable effects due to the carrier are substantially reduced in the present invention."

The Examiner has not been persuaded by this argument since the instant claims do not recite any particular amount of carrier in the formulation.

Next, Appellant urges, "The claimed invention does not contain any organic solvents. In contrast, the cited prior art contains organic solvents. Even the 'minimal side effects' caused by the organic solvents alluded by the Examiner are completely avoided by the present invention."

These arguments were not found persuasive. The Examiner notes that the instant claims utilize "comprising" claim language and thus permit the inclusion of additional unrecited elements, such as organic solvents. Moreover, one of ordinary skill familiar with this art would be fully capable of determining suitable solvents, which do not provide for adverse effects, but only positive effects, based on the desired or intended purpose at hand. The prior art ingredients allow for stable emulsions and thus would not be deemed detrimental to the formulation itself.

Appellant urges, "Davis teaches clear limits to the drug concentrations, i.e., the solubility of the drug. For example, Davis discloses up to 1 mg/ml, preferably 0.5 mg/ml of Amphotericin (col. 4, lines 14-16). Davis only teaches to dissolve the drug in amounts up to the saturation concentration of the drug in the oil and water."

The Examiner has not been persuaded by this argument. Davis does not teach 'clear limits' as urged by the Appellant, but rather, Davis teaches that the "level of drug may be chosen by one skilled in the art to suit the dosage regimen and so on but may *typically* be up to 1

mg/ml." (see col. 4, lines 14-16). The term "typically" is an equivalent and suggested term, which is not deemed to be limiting in any manner. The art teaches a suggested amount that does not set any particular limits.

Next, Appellant urges, "A main difference overlooked by the Examiner is the achieved drug loading: (1) the saturation concentration with Davis and Kaufman; and (2) in the supersaturation range in the present invention. In the present invention, going beyond the saturation limit and even doubling the saturation solubility is unexpected and something which is not predictable from Davis. Davis does not teach supersaturation of drugs."

These arguments were not found to be persuasive. The prior art desires "reduced toxicity" of the drug, as desired by Appellant (see Davis Abstract). No unexpected results are observed from the increased drug amounts, as urged by Appellant.

Appellant urges, "The Examiner is not correct in stating that the prior art teaches suitable concentrations to arrive at stable emulsions. The prior art concentrations are not sufficiently high to obtain acceptable injection volumes. The previous emulsions are even below the saturation concentration, i.e., they are not supersaturated emulsions. The emulsions of the invention are also stable, but the key feature is the supersaturation, which provides suitable injection volumes."

The Examiner has not been persuaded by this argument. The Appellants have not demonstrated that the concentrations taught by the prior art are not suitable or effective concentrations. Moreover, the prior art teaches and achieves the same objectives as instantly desired by Appellants, which is to provide "stable" drug emulsions. See Abstract of Davis, wherein Davis states that the emulsions are stable and reduce the toxicity of the drug.

With respect to Kaufman et al., the Appellant urges, "In the present invention, all side effects due to the organic solvents are avoided since no organic solvents are present. The prior art does not teach or suggest avoiding all side effects by using a composition containing no organic solvents."

These arguments were not found to be persuasive. A review of Applicant's specification at page 9, lines 6-9 indicates that 'for stabilization of the dispersions, emulsifiers and stabilizers can be used. These are possibly already contained in the emulsion used to produce the dispersion according to the invention, addition of further emulsifiers and stabilizers can be advantageous in the production of the dispersion'. Various emulsifiers, such as surfactants are also listed at page 9, lines 11-23. The arguments were not persuasive since the scope of the instant claims does not address the scope of Applicant's invention. Emulsifiers, surfactants and stabilizers are all permitted by the scope of the instant claims. Typical concentrations are 0.1-20% (see pg. 9, line 22). Thus, the argument that 'no organic solvents are present' is not persuasive.

Lastly, Appellant urges, "Davis and Kaufman do not disclose that the active drug can be present in solid crystalline form as recited in claim 2. Davis and Kaufman both require that the drug be dissolved, which is in a direction opposite to that of solid drug crystals. Davis and Kaufman do not teach how to make a dispersion containing the active ingredient dissolved in quantities greater than a factor of 1 (normal solubility) and cannot make obvious a supersaturation at a factor of 2, 5 and 10 times the normal solubility. Claims 149-150 recite the language 'organic solvent-free' and the Examiner has not made a *prima facie* case of obviousness."

These arguments were not found to be persuasive. Applicant's claims do not require the subsequent dispersion of the oil-in-water emulsion or a water-in-oil emulsion subsequently in water. The specification teaches this procedure at page 10, lines 26-36, but the instant claims do not require that. If Applicant has a dispersion in the presence of emulsifiers, stabilizers and surfactants, it is the position of the Examiner, that absent a direct comparison of the prior art, renders the instant dispersions obvious. There is no distinction between the dispersions being claimed and those in the art, other than the degree of the dissolved active ingredient. Applicant's desired properties are a) stability and b) reduced toxicity. The prior art's desired properties are also stability and reduced toxicity. The described differences are of degree and not of kind. The prior art clearly recognizes Applicant's desired properties. Hence, no unexpected results are seen in the 'supersaturated' dispersions as recited in the claims that would *patentably* define over the cited references. Thus, the Examiner believes that the instant invention is rendered *prima facie* obvious over the prior art of record.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Humera N. Sheikh - Art Unit 1615

hns
October 18, 2004

THURMAN K. PAGE, M.A., J.D.
SUPERVISORY PATENT EXAMINER

JYOTHSNA VENKAT
PRIMARY EXAMINER
GROUP 1500 1600

Conferees
Thurman K. Page (SPE)
Humera N. Sheikh

MANELLI DENISON & SELTER
2000 M STREET NW SUITE 700
WASHINGTON, DC 20036-3307